

Amendments to the Claims:

1-20. (Canceled).

21. (Currently Amended) A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

~~introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain~~ contacting the PAS domain with a small organic compound, whereby the compound enters the hydrophobic core of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B, and the binding specificity is an intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by ¹H/¹⁵N-HSQC NMR, wherein PAS refers to Per-ARNT-Sim, ARNT refers to acyl hydrocarbon receptor nuclear translocator, and HIF2a refers to hypoxia inducible factor 2 alpha.

22. (currently amended/withdrawn) A method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

~~introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain~~ contacting the PAS domain with a small organic compound, whereby the compound enters the hydrophobic core of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B and is present as part of HIF2a, and the binding specificity is an intermolecular binding affinity of the PAS domain detected as a change in transcription complex formation of DNA: the HIF-2a: ARNT.